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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/762,836	RISS ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *15-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-84 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-14) and of the species: first enzyme, second enzyme, first substrate, second substrate, sample, and fluorogenic product as caspase 8, LETD-aminoluciferin, caspase-3, DEVD-rhodamine-110, cell lysate, and rhodamine-110 respectively, in the reply filed on 01/30/06 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-III are closely related, and that a search of all the inventions would present no serious search burden, and that the Groups are in the same class. This is not found persuasive because the presence of a third enzyme potentially present in Groups II and III would significantly broaden the search beyond the metes and bounds of Group I. Further, the presence of a third enzyme provides Groups II and III with a separate design and mode of operation such that the Groups are independent and distinct from one another. Though the Groups may be classified in the same class, it is noted that class-based searches are no longer the norm, being replaced with text-based searching.

Claims 15-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/30/06.

The requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-14 were examined on their merits.

Specification

The use of the trademarks Dynex MLX, Fluoroskan Ascent, Texas Red, Bodipy, Caspase-Glo reagent and buffer and Beta-Glo reagent and Buffer has been noted in this application. They should be capitalized wherever they appear and be accompanied by the *generic terminology*.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the detection of multiple enzymes in genetically modified murine cells, does not reasonably provide enablement for all species of possible prokaryotic and eukaryotic organisms which may or may not have been transfected or genetically modified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 13 USPQ2d, 1737 (1990), and *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

In re Wands stated that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. While all of these factors are considered, sufficient amounts for a prima facie case are discussed below.

The instant specification alludes to the claimed invention as being practicable to an enormous range of cells, lysates, and combinations thereof. However, nowhere in the specification is the ordinary artisan directed or guided on how to apply the invention to such a wide range of disparate samples. The working examples provide only one example using genetically modified Chinese Hamster Ovary cells, while the ordinary artisan is expected to be able to immediately make and use the claimed invention on anything from mosquito larvae, pine tree bark, chimera cells or fungi. The level of skill in the art is deemed to be high, with predictability of the art regarding enzymes and their known substrates is high, however it is believed that the practice of the entire scope of the claimed invention would inevitably lead into the realm of undue experimentation by the ordinary artisan.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404).

The specification, while being enabling for the detection of multiple enzymes in genetically modified mammalian cells, does not reasonably provide enablement for all species of possible prokaryotic and eukaryotic organisms that may or may not have been transfected or genetically modified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 in line 1 states, "a method to detect the presence or *amount of* a first molecule for a first enzyme mediated reaction and a second molecule for a second enzyme mediated reaction", and in line 8 states "detecting the presence *or amount* of the first and the second molecules in the sample." Nowhere, in the claims or in the instant disclosure is taught the measurement of a quantifiable *amount of* enzyme, substrate or cofactor. The teachings and examples in the instant specification provide a means for detecting the presence of and quantification of the *amount of activity* of certain enzymes and the detection of already known amounts of enzyme, substrate and/or cofactor. Applicant appears to equate a measurement of the activity of a substance with a measurement or quantification of an unknown amount of that substance (Specification (Pg17, Line 27).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitations "first enzyme" and "second enzyme" in lines 5 and 6 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Bronstein *et al.* (6,586,196 B1).

Bronstein *et al.* teaches a method to measure the activity of a first enzyme for a first enzyme-mediated reaction and a second enzyme for a second enzyme mediated reaction, comprising;

Contacting mouse NIH/3t3 cells with a reaction mixture for the first reaction and for the second reaction, wherein a reaction mediated by the enzyme alkaline phosphatase (ALP) yields luminogenic byproduct and wherein a reaction mediated by the enzyme luciferase yields, in part, luminogenic and non-luminogenic products, the amount of activity of ALP and luciferase was detected and quantified (Column 20, Lines 20-37 and Fig. 1).

It is inherent in the reaction mediated by luciferase on the substrate luciferin, that products of that reaction include the non-luminogenic compounds of Carbon Dioxide, Adenosine Monophosphate, and Pyrophosphate, and that giving the claim its broadest reasonable interpretation, that all of the limitations of claims 1, 4, and 5 are met by the teachings of Bronstein *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein *et al.* (6,586,196 B1) in view of Mandlekar (2000).

Bronstein *et al.* teaches a method to detect the amount of activity of first enzyme for a first enzyme-mediated reaction and a second enzyme for a second enzyme-mediated reaction, comprising:

a) contacting a rodent cell lysate with a reaction mixture for the first reaction and for the second reaction, wherein a reaction mixture mediated by the first alkaline phosphatase yields a luminogenic product, and wherein a reaction mediated by the second luciferase yields both a luminogenic and non-luminogenic byproducts; and b) detecting the activity of the first and the second enzymes in the sample (Column 20, Lines 20-38, Fig. 1 and Column 23, Claim 1).

Bronstein *et al.* teaches a method wherein the first molecule is an enzyme for the first enzyme-mediated reaction, and wherein the second molecule is an enzyme for the second enzyme-mediated reaction (Column 20, Lines 20-38).

Bronstein *et al.* teaches a method wherein luminescence is employed to detect the first enzyme, and wherein the activity of the first and second enzymes is detected sequentially by contacting the lysate sample with the reaction mixture for the first reaction before the reaction mixture for the second reaction (Column 20, Lines 20-38).

Bronstein *et al.* teaches a method wherein the sample is contacted with the reaction mixture for the second reaction before the reaction mixture for the first reaction (Column 22, Lines 15-50).

Bronstein *et al.* does not teach wherein the first and second molecules are substrates for the first and second enzyme mediated reactions respectively.

Bronstein *et al.* does not teach wherein the first and second molecules are co-factors for the first and second enzyme-mediated reactions respectively.

Bronstein *et al.* does not teach wherein fluorescence is employed to detect the second molecule.

Bronstein *et al.* does not teach wherein the sample is contacted with the reaction mixture for the first reaction and the second reaction at the same time.

Mandlekar *et al.* teaches detecting the activity of at least a first enzyme for a first enzyme-mediated reaction and at least a second enzyme for a second enzyme-mediated reaction, comprising:

a) contacting a cell lysate simultaneously with a reaction mixture for at least the first reaction and for the second reaction, wherein a reaction mixture mediated by the first enzyme (caspase 1, 3, 6, 8) yields the fluorescent product AMC, and wherein a reaction mediated by the second enzyme (caspase 9) yields a fluorescent product AFC; and b) detecting the activity of the first and the second enzymes in the sample (Pg. 5996, Lines 35-44 and Pg. 5997, Fig.3a).

While enzyme cofactors and substrates are not specifically detected either in presence or activity in either reference, it is well known in the art that certain enzymes require the presence of particular cofactors and substrates in order to catalyze a reaction. If these cofactors and substrates are not present in the reaction, the reaction cannot proceed and no color or light reaction will be generated. These substrates, co-factors and their corresponding enzymes would be familiar to the ordinary artisan with a typical level of skill in the art at the time of the invention. For example, the enzyme Firefly luciferase requires the co-factors oxygen, ATP, and Magnesium in order to catalyze its substrate luciferin. Since both references' enzyme reactions were successful, it is obvious that the ordinary artisan would recognize by deduction that the proper cofactors and substrates were present in the methods taught by the references.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Bronstein *et al.* with those of Mandlekar *et al.* because this would enable one of ordinary skill to simplify the method as taught by Bronstein *et al.* making it more time and cost efficient.

The ordinary artisan would have been motivated to combine the two teachings to arrive at a dual luminogenic/fluorescent assay because the generated luminescence would serve as a visible control for the reactions proceeding correctly and the elimination of a second luminogenic enzyme and substrate would enable the artisan to skip the steps of inactivating the first enzyme through pH, heat, or addition of an inhibitor which could serve to interfere with the proceeding of the second enzyme-mediated reaction.

The ordinary artisan would have had a reasonable expectation of success in combining the two methods due to the individual success of the methods taught by Bronstein and Mandlekar and the fact that non-luminogenic substrates are well known and defined in the art of multiple enzyme analyses.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one with ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence or evidence to the contrary.

No Claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gurtu *et al.* FLUORIMETRIC AND COLORIMETRIC DETECTION OF CASPASE ACTIVITY ASSOCIATED WITH APOPTOSIS; Analytical Biochemistry, Vol. 251 (1997) pp. 98-102.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Paul Martin
Examiner
Art Unit 1655

03/07/06

PATRICIA LEE
PRIMARY EXAMINER